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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/031,478

07/29/2002

Kevin Jeffrey Barnham

16153

8704

23389 7590 06/20/2007
SCULLY SCOTT MURPHY & PRESSER, PC
400 GARDEN CITY PLAZA
SUITE 300
GARDEN CITY, NY 11530

EXAMINER

KOSAR, ANDREW D

ART UNIT

PAPER NUMBER

1654

MAIL DATE

DELIVERY MODE

06/20/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/031,478	Applicant(s) BARNHAM ET AL.	
	Examiner Andrew D. Kosar	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 April 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 31-41, 44 and 45 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31-41, 44 and 45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
5) <input type="checkbox"/> Notice of Informal Patent Application
6) <input type="checkbox"/> Other: _____ |
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DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 12, 2007 has been entered.

Allowable Subject Matter

Applicant's elected species (NiTPP-VLFFA) has been previously indicated as free of the prior art (*see Office Action 4/26/06*).

Response to Amendment/Arguments

Applicant's amendments and arguments filed April 12, 2007 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Claim Objections

Claim 34 is objected to because of the following informalities: the term 'loop' is misspelled 'lop'. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 31-40 and 45 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. As drafted, the process can be reasonably interpreted as

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being a naturally biological process, e.g. circulating hemoglobin, ceruloplasmin, and insulin contacting amyloid protein in the brain.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-41, 44 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated that, "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the

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claimed invention.” Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.” *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated that, “A written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) (“In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...”) *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is “not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.” MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not

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constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include “level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.” MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to inhibiting the binding of metal ions to the β -amyloid peptide, or treating Alzheimer’s disease with a metal complex

(1) Level of skill and knowledge in the art:

The level of skill and knowledge in the art is low, particularly with regards to the *a priori* knowledge of which metal complexes will, or will not, function in the methods as claimed.

(2) Partial structure:

The claims require that the compounds only be a metal complex. The specification provides several compounds that are asserted to function as claimed, providing BRI7161, BRI7159, BRI7158, BRI7080 or BRI7103.

(3) Physical and/or chemical properties and (4) Functional characteristics:

The compounds must be a metal complex and inhibit the binding of metal ions to the β -amyloid peptide, and thereby be used in treating Alzheimer's disease.

(5) Method of making the claimed invention:

Methods of making metal complexes are known to the artisan, however methods of making the myriad of compounds that will be capable of functioning as required in the claims is beyond that of the skilled artisan. One would not know which compounds to make to practice the method as claimed beyond BRI7161, BRI7159, BRI7158, BRI7080 or BRI7103.

As stated supra, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 31-31, 44 and 45 is/are broad and generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any metal complex. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus. While having written description of BRI7161, BRI7159, BRI7158, BRI7080 or BRI7103 and compounds specifically identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention

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achieves and the problems the invention will hopefully ameliorate.”) Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claims 31-41, 44 and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the binding of metal ions to β -amyloid peptide with BRI7161, BRI7159, BRI7158, BRI7080 or BRI7103 or the compounds specifically identified in the prior art, does not reasonably provide enablement for inhibition of the binding of metal ions to the β -amyloid peptide, or treating Alzheimer’s disease with all metal complexes.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in *Wands* states, “Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is ‘undue’, not ‘experimentation’” (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. “Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations” (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

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(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to inhibiting the binding of metal ions to the β -amyloid peptide, or treating Alzheimer's disease with a metal complex. Thus, the claims taken together with the specification imply one could treat Alzheimer's with any metal complex and inhibit the binding of metal ions to the β -amyloid peptide with a metal complex.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the art with regards to treating Alzheimer's is unpredictable.

WebMD (WebMD Alzheimer's Disease: treatment overview. Web document <<http://my.webmd.com/content/article/71/81399.htm>> Accessed 2/22/05. 2 pages) teaches that, "there is no cure for Alzheimer's disease and no proven way of slowing its progression. Because the exact cause of Alzheimer's disease is unknown, there is also nothing that can be done to prevent it." (page 1 of 2).

WebMD teaches that the approved drugs for treatment, "Aricept®, Exelon®, Reminyl®, and Cognex® seem to help only those with mild or moderate symptoms of Alzheimer's disease; Namenda® is prescribed for patients who have moderate-to-severe Alzheimer's." (page 2 of 2). The approved drugs are all for slowing the breakdown of acetylcholine.

Further, ADEAR (ADEAR Alzheimer's Disease Medications fact sheet. NIH Publication 03-3431. Alzheimer's Disease Education & Referral Center. National Institute on Aging, NIH, US Dept HHS. July 2004. 6 pages) teaches that Aricept®, Exelon®, Reminyl®, and Cognex® are for mild to moderate Alzheimer's disease (column 2), and Namenda® is for moderate to severe Alzheimer's (column 3).

Although these compounds are approved for treating Alzheimer's, Ballard (C Ballard, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease : randomized double blind placebo controlled trial. British Medical Journal. (2005) February 18, 5 pages) teaches that rivastigmine (Exelon®, supra), "seemed of no benefit in patients with dementia and agitation in institutional care," and that quetiapine "was associated with greater cognitive decline than placebo." (page 4 of 5).

Furthermore, treating Alzheimer's necessarily requires delivery of the therapeutic to the brain, however EVERTS (S. Everts, "Brain Barricade". C&E News (2007), 85(23), pages 33-36, html copy, 6 pages) teaches, "Conditions of neurodegeneration are not well-served by current therapies, and they place a tremendous burden on our society," and, "Crossing the BBB is certainly not impossible, but it remains a significant challenge." (page 6 of 6).

(5) The relative skill of those in the art:

In view of the art, the level of skill in the art is low, such that one would not know which metal complex compounds would work in the methods as claimed.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided compounds asserted to be useful in the methods. The specification provides in vitro testing and ex vivo (e.g. NMR) testing for several compounds. However, the specification does not provide sufficient guidance, including examples, working or prophetic, to show that any of the compounds work in treating Alzheimer's beyond BRI7161, BRI7159, BRI7158, BRI7080 or BRI7103.

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(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to treating Alzheimer's and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Claim Rejections - 35 USC § 102

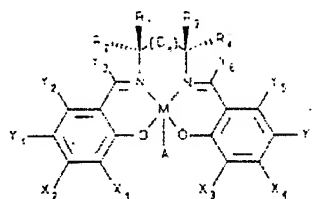
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-37, 40, 41, 44 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by MALFROY-CAMINE (WO 96/40148 A1).

The instant claims are presented *supra*. Malfroy-Camine teaches a method for preventing, arresting or treating a free radical-associated disease state by administration of a



salen metal complex of the general formula: (M=Mn, Co, Fe, V, Cr or

Ni) where the disease is Alzheimer's (e.g. claim 6). Because the compound meets the structural requirements and is administered to the same patient population, it inherently must function as claimed, i.e.- blocking binding of the metal ions to the β -amyloid peptide, etc. Additionally, please note, since the Office does not have the facilities for examining and comparing Applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art.

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See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980), and “as a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith.” *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31-41, 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malfroy-Camine, *supra*, in view of PARDRIDGE (US Patent 5,004,697).

The instant claims and teachings of Malfroy-Camine are presented *supra*.

Pardridge teaches modifying antibodies for delivery through the BBB for neuropharmaceuticals (e.g. Abstract, claims 6 and 9), specifically teaching that the antibody is for amyloid peptide of Alzheimer's disease (claim 9).

The difference between the instant claims and the teachings of Malfroy-Camine, is that while Malfroy-Camine teaches treating Alzheimer's with a metal salen complex, Malfroy-Camine does not teach coupling it with a targeting moiety.

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It would have been obvious to have made and delivered the metal salen complex via coupling to an amyloid specific antibody in order to specifically deliver the salen complex to the Alzheimer's plaques it is used to treat. One would have been motivated to have coupled the salen to an antibody in order to deliver the salen complex efficiently to the point of need. One would have had a reasonable expectation for success in making a salen-antibody conjugate, as conjugation of antibodies to therapeutics is a technique widely practiced in the medicinal arts, particularly to cross the BBB (e.g. Saito, et al. PNAS (1995) 92, pages 10227-10231).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


Andrew D Kosar

Patent Examiner, Art Unit 1654